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SARCOIDOSIS SIMULATING GLOMERULONEPHRITIS

HARRY F. KLINEFELTER, JR., MAJOR, M.C.[1] AND
S. MARION SALLEY, LT. COL., M.C.

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Sarcoidosis, originally described by Boeck, is now recognized to be a generalized granulomatous disease of unknown cause which may involve any part of the body. During the last 10 years, many articles have been published dealing with the protean manifestations of the disorder, and it is now well recognized that skin lesions are only a minor and inconstant manifestation of the disease. Renal involvement accompanied by extensive retinal changes is so unusual in sarcoidosis that a case of this type is being reported in some detail.

REVIEW OF THE LITERATURE

Schaumann (1) was the first to find lesions of sarcoidosis in the kidneys of one of his patients who died with heart-failure after an illness lasting for 16 years. The patient, however, had no symptoms of renal disease. Spencer and Warren (2), in 1938, found lesions in the kidneys of a 51 year old man who died after an illness of 3 years' duration. This patient likewise had no symptoms of renal diesase. In 1939 Horton, Lincoln, and Pinner (3) reported the case of a 42 year old man with an 11 year history of sarcoidosis who died with a terminal pulmonary tuberculosis. During the last two years of his life he had albuminuria, diminished PSP excretion and reduction of urea clearance. NPN was elevated and the blood pressure was normal. Autopsy showed miliary caseated tubercles and epitheloid cell granulomata in the kidneys. There were also degenerative changes in the epitheloid cells of the proximal convoluted tubules with globular degeneration, swelling, loss of nuclei, and granular and homogenous casts. Other tubules were shrunken and calcified. The kidneys weighed 81 and 83 gms., were small and scarred and the cortices were thinned.

Hollister and Harrell (4) in 1941 described another patient who had

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both sarcoidosis and tuberculosis. This patient had no symptoms of renal disease but at autopsy typical sarcoid lesions were present in the left kidney. Longcope (5) in 1941 reported 31 cases, in 4 of which autopsy was performed. In 3 of these 4 cases lesions were present in the kidneys, but had apparently caused no signs or symptoms.

Salvesen (6) in 1935, reported 4 cases in great detail to illustrate that sarcoidosis is a generalized disease. One of his patients, a woman of 58, had had skin lesions for 10 years when at 55 she developed failure of vision, fatigue, polyuria and a dry cough. Bilateral optic neuritis and albuminuria were discovered. She had slight fever, normal blood pressure, 95/55, and a severe anemia. Urine contained small amounts of albumin, granular casts, and leukocytes and was of low fixed specific gravity. Blood urea was 100 mgms. and PSP excretion was 5% in 2 hours. Over a period of 2 years her vision improved greatly but further study of kidney function could not be obtained. At the time the case was reported, the patient was living and apparently well, illustrating that the prognosis in sarcoidosis is generally good. Typical x-ray changes were present in the chest and the tuberculin test was negative.

In 1942, Rotenberg and Guggenheim (7) reported a 24 year old white man who had had typical sarcoidosis for several years, proven by biopsy. At 23 he developed nausea, vomiting, nocturia and burning on urination. He was found to have albuminuria with casts and leukocytes in the urine. Blood pressure was elevated, 154/115, and there was evidence of marked impairment of renal function. PSP excretion was 9% in 2 hours, NPN was 70 and the specific gravity of the urine was fixed at a low level. This patient was under observation for a year during which time the evidence of renal insufficiency did not improve. He also had a duodenal ulcer, a palpable spleen and evidence of myocardial involvement with prolongation of the P-R interval. X-ray of the chest showed extensive changes typical of sarcoidosis.

Goldberg and Newell (8) have recently reported sarcoidosis with retinal involvement in two young male negro soldiers. These patients had extensive retinal vascular lesions, and later developed large proliferative lesions, presumably sarcoid granulomata, near the disk. The retinal vascular lesions involved the veins which were constricted

and irregular in caliber. Some veins were thrombosed and replaced by fibrous bands. Numerous deep and superficial flame-shaped retinal hemorrhages and a few vitreous hemorrhages were present. In one patient, all retinal hemorrhages disappeared without residue and vision improved markedly. Both patients showed generalized lymphadenopathy, parotid swelling, the typical pathologic picture on biopsy, and were insensitive to 1 mgm. of tuberculin.

REPORT OF CASE

R. W., a 23 year old unmarried negro soldier, enjoyed excellent general health until December 1944.

Family history was non-contributory. *Past history* revealed that he had been born and reared on a farm in North Carolina. He had whooping cough and measles in childhood, chicken pox and gonorrhea in 1943, and recovered uneventfully from these infections. He was inducted into the Army on 20 October 1942 and went overseas to Italy in October 1944.

Present illness began insidiously in December 1944 when he began to have nocturia. This gradually increased to 4–5 times a night and he slowly lost weight. In March 1945 he developed headaches, vertigo, blurring of vision, easy fatigue and exertional dyspnea. He had lost 50 lbs. when he was hospitalized on 17 April 1945. At that time he had low grade fever, a severe retinitis with engorgement and distention of the veins, and retinal hemorrhages and exudates. The urine contained albumin with granular casts and cellular elements, but the blood pressure was normal, ranging from 110/70 to 130/80. A moderate anemia and nitrogen retention were found and he was evacuated to the Z.I., arriving at Battey General Hospital on 18 June 1945.

Physical examination: T-100°, P-98, R-20, B.P. 116/76. The patient was a well-developed but markedly undernourished, severely and chronically ill, dark-skinned negro, with pallor of the mucous membranes and a uriniferous breath. Vision was greatly impaired. Pupils were equal and active to light. The fundi showed haziness of both disks, with marked compression of the retinal veins. 2–3 diameters from the disk, many veins were thrombosed and some were replaced by irregular white strands of tissue. Small spindle shaped hemorrhages were present, and on the right a complete macular star. The femoral and inguinal lymph nodes were greatly enlarged, and there was slight enlargement of the cervical, axillary, and epitrochlear nodes. All nodes were firm, discrete, and not attached to underlying skin. The lungs were clear. The heart was normal in rate, rhythm and size and there were no murmurs. Liver and spleen were not enlarged. The remainder of the physical examination was negative.

Laboratory examinations showed a normochromic, normocytic anemia, with hematocrit reading of 32. WBC was 6,000 with normal differential, and sedimentation rate was elevated, 30 mm. per hour (Wintrobe). Urine was of low

specific gravity, and contained a trace of albumin, occasional red cells, leukocytes, and granular casts. NPN was 76 mgm. %. Total serum proteins were 8.2 gm. with albumin 3.0 gm. and globulin 5.2 gm. per 100 cc. Intravenous P.S.P. test showed 20% excretion in 15 min., and a total of 35% in 45 min. Fishberg concentration test showed maximum specific gravity of 1.012.

Patient was put on absolute bed-rest and treated as a chronic nephritic, with transfusions and a high caloric, low salt diet supplemented with vitamins. He ran a remittent fever, up to 102° in the evening, ate poorly, and the general glandular enlargement increased. On 9 July 1945, one of the enlarged left femoral nodes was removed. This showed the typical microscopic picture of sarcoidosis (Fig. 1, A and B), with hard tubercle formation and epitheloid cells, without caseation. The biopsy wound healed promptly, but was followed by a persistent underlying fluctuant swelling. This swelling was aspirated on several occasions; it contained sterile serum and gradually subsided over a period of 1 month. The patient's vision began to improve, the disks became less blurred and the distention of the retinal veins diminished. Temperature elevation decreased, but the renal insufficiency showed no improvement, and his general condition grew worse. Tuberculin test was negative to 2nd strength PPD and x-ray of the chest was clear.

In early August, serum calcium was found to be 17.4 mgm. % and the serum phosphorus 4.3 mgm. %. Complete skeletal x-rays showed no bone lesions. Patient was put on a low calcium diet, fluids were forced, and he was allowed to be out of bed. This increased activity appearently caused a slight temporary increase in fever but his general condition improved, with return of appetite and slow gain in weight. Although calcinuria was only 200 mgm. in 24 hours, the serum calcium promptly decreased but remained elevated, circa 13 mgm. % and the serum phosphorus remained around 4 mgm. %.

During the next three months his temperature slowly fell to normal, vision improved, and the lymph nodes decreased in size. Blood pressure was never elevated, remaining about 120/80. He received large doses of saturated solution of potassium iodide, with no apparent benefit. NPN ranged from 50 to 90, serum proteins from 8 to 10.5 gm., with constant increase in globulin. Urine continued to show small amounts of albumin, low fixed specific gravity, and occasional cellular elements and casts. Urea clearances were 40% of normal in September and 32% of normal in November. P.S.P. excretion in November was 10% in first 15 minutes with a total of 20% in 45 minutes. The normocytic, normochromic anemia persisted, with the volume of packed red cells ranging from 33 to 37. Total white blood count was always within normal limits; the differential occasionally showed an increase in eosinophiles, as high as 6%.

Although vision steadily improved, impairment of vision persisted, due to fibrosis and scarring, particularly in the region of the right macula. The haziness of the disks completely disappeared, but perivascular sheathing of the veins persisted. The patient complained chiefly of itching, but no skin lesions were present, and it was felt that the pruritus was the result of the uremia. He developed a mild dry cough, but physical examination and x-ray of the lungs were normal.

Blood cultures, stools, electrocardiograms, spinal fluid, I.V. urogram, serum

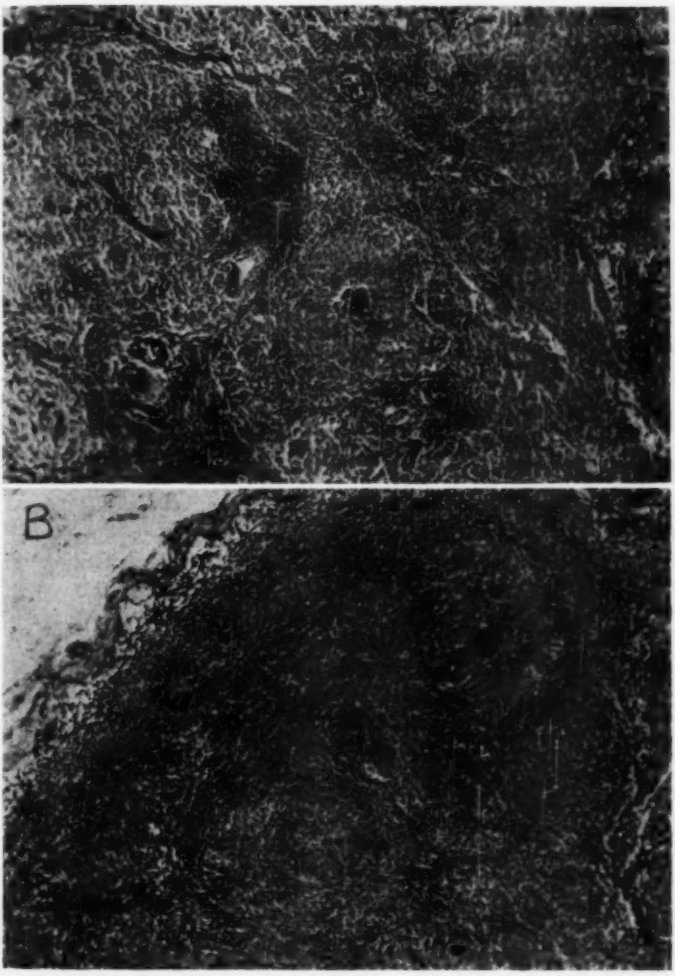

FIG. 1. LEFT FEMORAL LYMPH NODE. TYPICAL PATHOLOGIC HISTOLOGY OF SARCOIDOSIS

A. (top)—low power magnification.
B. (below—high power magnification.

cholesterol, alkaline phosphatase, Frei test, Kahn test, test for Bence Jones protein in urine, and the test for sickling of the red blood cells were either normal or nega-

tive. The bones were repeatedly normal on x-ray examination and sternal bone-marrow biopsy showed no sarcoid involvement.

In October 1945, he was put on a regular diet with forced fluids, and his improvement continued. He was discharged from the Army on a Certificate of Disability on 7 December 1945 and transferred to a Veterans Administration Facility.

Follow-up reports from the Veterans Administration indicate that renal function slowly improved. When patient was discharged home in February 1946, NPN had fallen to 43 and Fishberg test showed maximum specific gravity of 1.020, although urine still contained albumin and occasional hyaline and granular casts. In March 1946, the patient was admitted to another V.A.F. because of weakness and numbness of the lower extremities. A routine urinalysis was reported as "perfectly normal and of good specific gravity." No further kidney function studies were performed. Chest x-ray was negative. Symptoms and signs of nervous system involvement slowly subsided and he was discharged home in May 1946.

Summary: A 23 year old negro soldier developed nocturia in December 1944; weight loss, headaches, and visual impairment gradually appeared. In April 1945, fever, retinitis, anemia, albuminuria, and azotemia with normal blood pressure were found. In June, enlarged lymph nodes were biopsied and showed sarcoidosis. Hypercalcemia, hyperglobulinemia, and insensitivity to tuberculin were present. During the next 10 months, fever, lymphadenopathy, and retinal changes subsided; hypercalcemia decreased; anemia and renal insufficiency improved.

DISCUSSION

Renal insufficiency is a relatively uncommon finding in sarcoidosis and only 3 other cases could be discovered in an extensive review of the literature. In Table 1, the pertinent data in these 3 cases and the present case are tabulated. There is ample evidence that all these patients had generalized sarcoidosis, although only in case 1 was an autopsy performed and actual renal involvement proven.

These four cases of "renal sarcoidosis" are quite similar, with relatively long benign course, minimal urinary findings with azotemia, anemia, and usually, normal blood pressure. In case 3, the blood pressure was apparently taken only on admission, and the moderate elevation may not have been sustained on further examinations. In all patients, the degree of retention of non-protein nitrogen with anemia seems out of proportion to the clinical evidence of renal disease. The clinical picture in general resembles chronic pyelonephritis but is not typical of any of the common types of nephritis.

TABLE 1

Renal Sarcoidosis

CASES	AUTHOR	AGE	SEX	RACE	DURATION OF SYMPTOMS	B.P.	AZOTEMIA	UREA CLEARANCE	P.S.P.	URINALYSIS	OTHER MANIFESTATIONS
1	Horton, Lincoln and Pinner	42	M	W	2 years	122/80	NPN 78–84	55–47	22% in 2 Hr.	S. G. low, fixed. Albuminuria, casts.	Anemia, adenopathy, skin lesions, bone changes, lung lesions. Terminal pulmonary tbc. Autopsy showed both sarcoid and tuberculous renal lesions.
2	Salvesen	56	F	W	3 years	95/55	Urea N. 47		5% in 2 Hr.	S. G. 1.006–1.010. Albuminuria, casts.	Anemia, optic neuritis, skin lesions, fever, lung lesions, negative tuberculin.
3	Rotenberg and Guggenheim	24	M	W	1.5 yrs.	154/115	NPN 61–70		9% in 2 Hr.	S. G., low, fixed. Albuminuria, casts.	Anemia, adenopathy, lung lesions, splenomegaly, prolonged P-R interval, duodenal ulcer.
4	Klinefelter and Salley	23	M	C	1 year	116/76	NPN 50–90	32	35–20% in 45 min.	S.G. 1.007-1.012. Albuminuria, casts.	Anemia, adenopathy, extensive retinal lesions, fever, hyperglobulinemia, hypercalcemia.

It seems probable that the renal insufficiency in sacoidosis is the direct result of invasion of the kidneys by sarcoid granulomata. Longcope (5) originally emphasized that the clinical manifestations of the disease are more the result of mechanical than toxic factors. Cases 2 and 4 did have fever for a time, which might be interpreted as evidence of toxicity; but in case 4, the renal insufficiency showed no improvement as the fever subsided. It appears that renal insufficiency is primarily the result of actual mechanical interference with kidney function.

In case 4, the retinal lesions were not typical of those usually found in nephritis. The arteries were little if at all involved; the veins completely bore the brunt of the pathological changes. Futhermore, the retinal changes subsided while the renal insufficiency did not improve, which indicates that the retinitis was not due to the renal failure. Similar retinal changes have been found in other patients with sarcoidosis, with no renal damage, and will be reported in a subsequent paper (9). These patients had no large tumor masses in the fundus as did the patients described by Goldberg and Newell (8), but they had involvement of lungs and lymph nodes, proven by biopsy.

It is apparent, therefore, that extensive retinal changes occur in sarcoidosis, with or without renal involvement, and that the retinitis does not result from the renal damage. The mechanism of production of the retinitis in sarcoidosis is not understood.

It is extremely important to recognize sarcoidosis, since the prognosis in this disease is generally favorable. In cases 1, 2 and 3, in Table 1, the diagnosis was made before renal insufficiency developed. In case 4, however, the presenting signs were those of renal insufficiency with retinitis, and the correct diagnosis was made only when the unexplained fever and lymphadenopathy led to the performance of a biopsy. While the diagnosis of sarcoidosis can be made with certainty only on finding the typical pathologic histology (Fig. 1), the disease should be suspected when hyperglobulinemia and hypercalcemia are found in the presence of azotemia. Multiple myeloma is the only other disease which may cause this unusual blood chemical abnormality.

SUMMARY

1. A case of generalized sarcoidosis with renal insufficiency and retinitis is reported in detail.

2. Three other cases of sarcoidosis with renal insufficiency are reviewed and the findings in the 4 cases are tabulated.

3. The mechanism of the renal insufficiency in sarcoidosis is discussed.

4. Retinitis with or without renal involvement may occur in sarcoidosis.

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SULFONAMIDE SENSITIVITY DETERMINATIONS OF HEMOLYTIC STREPTOCOCCI ISOLATED FROM PATIENTS BEFORE AND AFTER TREATMENT WITH SULFADIAZINE[1]

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Recently reported epidemics (1, 2, 3) of streptococcal infections caused by sulfadiazine-resistant group A hemolytic streptococci, which appeared during mass chemoprophylaxis programs in the Armed Forces, have aroused interest as to the likelihood of drug-resistant strains developing during any form of drug therapy. It would be of practical importance to know whether the streptococci, infecting patients, develop any degree of sulfonamide resistance during the course of therapy with these drugs, and if it is possible to recover sulfonamide-resistant strains from convalescent carriers after such treatment. This report is concerned with the results of testing the sulfonamide sensitivity of hemolytic streptococci, present in the throats of patients, before and after therapeutic doses of sulfadiazine.

MATERIALS AND METHODS

The hemolytic streptococci used in this study were obtained from the nasopharynges of 40 patients admitted to this hospital during the spring, fall, and winter of 1942–43, which was prior to the time that mass chemoprophylaxis was instituted in the U. S. Navy on December 1, 1943 (4). With one exception all of these patients developed clinical evidence of scarlet fever.

Cultures from the nasopharynx were obtained on admission of the

[1] This investigation was carried out under a contract between The Rockefeller Institute for Medical Research and the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of The Surgeon General, United States Army.

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patient to the hospital while in the acute phase of the disease, and also in the convalescent period after a course of sulfadiazine therapy which was given either for treatment of purulent complications or in an attempt to prevent the development of a carrier state. Cultures were preserved by drying from the frozen state (5); and the group and type were determined by the precipitin technique (6). Sulfonamide sensitivity was determined by the method of Wilson (7).

The usual dosage schedule for the administration of sulfadiazine was 2.0 gm. as the initial dose and then 1.0 gm. every four hours for at least four doses during the first day of treatment; thereafter, the patient received 1.0 gm. every four hours for five doses during each day. Most of the patients also used a nose and throat spray of 2.5 per cent sodium sulfadiazine in glycerin and saline, as well as a 2.5 per cent sodium sulfadiazine gargle at frequent intervals during the acute phase of the disease. Five patients received 2 courses of sulfadiazine therapy; the remainder had only one course. Frequent determinations of the blood sulfadiazine concentration were made on each patient, according to the method of Bratton and Marshall (8).

In order to avoid cross infections, only patients harboring the same type of group A streptococci were allowed to be together in the same room; otherwise they were strictly isolated.

RESULTS

Group A streptococci were isolated from the nasopharynges of 39 patients, before and after sulfadiazine therapy; one patient had a group C infection. The different types of group A streptococci isolated are indicated in Table 1; type 19 was the predominating infecting organism.

In all patients, streptococci of the same type were recovered in both the acute and convalescent phases of the disease; therefore, the patient presumably carried the same type of hemolytic streptococcus throughout his course of therapy. This finding confirms the observations of others (9, 10) on the inability of sulfanomides to prevent the development of a carrier state. The time of taking the convalescent phase culture varied from the day following the cessation of the sulfadiazine treatment to several months following therapy (see Table 1).

The total amount of sulfadiazine administered during any single

TABLE 1

PATIENT	TYPE OF GROUP A STREPTOCOCCUS CULTURED FROM NASOPHARYNX	ACUTE PHASE CULTURE		SULFADIAZINE THERAPY			CONVALESCENT PHASE CULTURE*		
		Date of Isolation	Degree of Sulfadiazine Resistance	Date Started	Duration	Total Amount Received	Date of Isolation	Period Elapsed After Sulfadiazine Therapy	Degree of Sulfadiazine Resistance
			mg.		*days*	*gm.*		*days*	*mg.*
1	3	3/27/42	0	3/30/42	6	29	4/ 5/42	1	0
2	3	4/ 1/42	0	4/10/42	7	32	4/17/42	1	0
3	3	2/11/43	0	2/12/43	12	57	3/ 3/43	8	0
4	3	3/15/43	0	3/29/43	9	41	4/ 8/43	2	0
5	3	3/25/43	0	3/28/43	11	52	4/12/43	5	0
6†	6	2/ 6/43	0	2/ 5/43	10	52	3/10/43	13	1
				2/18/43	8	43			
7	6	3/ 1/43	1	3/14/43	5	25	9/ 7/43	173	1
8	18	5/ 6/42	0	5/19/42	7	28	5/27/42	2	0
9†	19	3/16/42	0	3/16/42	10	46.5	5/10/42	15	0
				4/23/42	3	14.0			
10	19	4/ 1/42	0	4/ 8/42	7	30	4/16/42	2	0
11	19	4/ 1/42	0	4/ 3/42	5	24	5/10/42	33	0
12	19	4/20/42	0	5/ 5/42	5	24	6/22/42	44	0
13	19	11/ 3/42	0	11/17/42	8	38.5	1/ 1/43	38	0
14	19	11/ 8/42	0	11/18/42	7	36	12/27/42	33	0
15	19	11/ 9/42	0	11/18/42	6	26	1/11/43	49	0
16	19	11/ 9/42	0	11/19/42	10	45	12/ 7/42	9	0
17	19	11/14/42	0	11/17/42	9	54	1/11/43	47	0
18	19	12/ 3/42	0	12/21/42	9	36	1/17/43	19	0
19	19	12/15/42	0	12/15/42	16	42	1/18/43	18	0
20	19	12/19/42	0	12/23/42	11	45	1/16/43	13	0
21	19	12/21/42	0	1/ 2/43	10	41	1/26/43	15	0
22†	19	12/29/42	0	1/ 6/43	14	58	2/ 3/43	1	0
				1/26/43	8	24			
23	19	1/ 2/43	0	1/10/43	8	35	2/ 1/43	15	0
24†	19	1/ 8/43	0	1/10/43	13	48	2/ 1/43	1	0
				1/26/43	6	18			
25†	19	1/18/43	0	1/18/43	5	21	2/28/43	11	0
				1/31/43	18	75			

TABLE 1—*Concluded*

PATIENT	TYPE OF GROUP A STREPTOCOCCUS CULTURED FROM NASOPHARYNX	ACUTE PHASE CULTURE		SULFADIAZINE THERAPY			CONVALESCENT PHASE CULTURE*		
		Date of Isolation	Degree of Sulfadiazine Resistance	Date Started	Duration	Total Amount Received	Date of Isolation	Period Elapsed After Sulfadiazine Therapy	Degree of Sulfadiazine Resistance
			mg.		*days*	*gm.*		*days*	*mg.*
26	19	1/26/43	0	1/31/43	9	42	2/15/43	7	0
27	19	2/ 5/43	0	2/ 8/43	12	62	2/21/43	2	0
28	19	2/ 8/43	0	2/20/43	10	56	3/ 8/43	6	0
29	19	2/ 8/43	0	2/17/43	13	66	3/ 9/43	8	0
30	19	2/16/43	0	2/27/43	8	46	3/17/43	10	0
31	19	3/11/43	0	4/28/43	10	45	5/10/43	3	0
32‡	26	3/20/42	0	4/14/42	10	49	5/14/42	21	0
33	30	5/ 4/42	0	5/19/42	6	24	5/28/42	4	0
34	30	5/25/42	0	6/ 9/42	5	23	6/14/42	1	0
35	30	5/28/42	0	6/ 9/42	5	23	6/15/42	2	0
36	30	12/26/42	0	1/ 8/43	10	41	1/20/43	3	0
37	33	4/20/42	0	5/ 5/42	5	24	5/15/42	6	0
38	38	3/13/42	0	4/ 1/42	6	27	4/ 7/42	1	0
39	NC§	2/21/43	0	3/ 4/43	13	66	3/20/43	4	0
40¶		1/26/43	0	2/ 5/43	10	44	2/15/43	1	0

* Since not all cultures isolated during the patients' illness were saved, the convalescent phase culture was the culture preserved nearest to the time of cessation of drug therapy.

† Patients who received two courses of sulfadiazine therapy.

‡ This patient did not develop scarlet fever.

§ NC indicates strain not classified by the precipitin method with available diagnostic sera.

¶ This patient was infected with a group C streptococcus.

period of treatment varied between 14 and 75 grams; and the number of days of treatment for any single course of therapy was between 3 and 18 days. The blood levels of sulfadiazine, while the patients were under treatment, ranged between 2.0 and 12.0 mg. per hundred cubic centimeters, with an average of 7.3 mg. per hundred cubic centimeters.

The acute and convalescent phase hemolytic streptococcus cultures

were tested for sensitivity to sulfadiazine according to the method of Wilson (7). This method enables one to determine the ability of hemolytic streptococci to grow in a semi-solid sulfonamide inhibitor-free medium containing respectively 0, 1, 5, 25, and 125 mg. per cent sodium sulfadiazine. As recorded in Table 1, none of the hemolytic streptococcus cultures tested for sensitivity to sulfadiazine showed any significant degree of resistance; i.e., none grew in a concentration of sodium sulfadiazine as great as 5 mg. per cent. However, in 3 instances a few colonies appeared in the medium containing sodium sulfadiazine in a concentration of 1 mg. per cent.

An attempt was made to detect even a slight tendency toward development of sulfadiazine resistance in the streptococci recovered from patients following a period of therapy. This was done by refining the usual technique for testing sulfonamide resistance as follows: tubes of Wilson's media were prepared which contained respectively 0.01, 0.05, 0.1, 0.25, and 0.5 mg. per cent sodium sulfadiazine, and were then inoculated in the usual manner with "pre-treatment and post-treatment" cultures. No consistent differences were demonstrated as to the ability of either type of inocula to grow in these media.

DISCUSSION

The results of this study demonstrate that hemolytic streptococcus cultures obtained from the nasopharynx of patients following sulfadiazine therapy did not develop any significant resistance to this drug. However, using the same criteria for the estimation of drug resistance as in this report, sulfadiazine-resistant hemolytic streptococci did, in fact, appear in the Armed Forces (1, 2) during programs of mass sulfadiazine prophylaxis.

In comparing the methods and results of this study and of those in the Armed Forces, several striking differences become apparent. In the present investigation, large daily therapeutic doses of sulfadiazine were used; drug concentrations in the blood averaged about 7.3 mg. per cent; and the periods of administration were relatively short, that is, of only a few days duration. In the Armed Forces, on the other hand, the patients received small daily prophylactic doses of 0.5 gm. or 1.0 gm. of sulfadiazine, which resulted in median blood levels of 1.4 mg. and 2.2 mg. per cent (9); the periods of administration were of several

months duration; and a continuing renewal of a susceptible population, such as occurs during emergency military activities, rendered conditions favorable for the propagation and spread of drug-resistant strains, once they were established.

Since the mechanism by which bacteria become resistant to drugs is not known, several theories have been proposed. Probably the most commonly mentioned explanations for the development of drug-resistant bacteria are that it is due to (a) mutation, induced either by environmental conditions or occurring as a natural phenomenon; or (b) adaptation, by means of which bacteria gradually acquire the ability to tolerate unfavorable environmental conditions following long periods of exposure to them. Whatever the mechanism for the development of drug-resistant bacteria, it would seem that conditions as they existed during mass prophylaxis programs, such as were carried out by the Armed Forces, might favor the propagation of drug-resistant hemolytic streptococci once they had developed. On the other hand, the development of drug-resistant strains of hemolytic streptococci during short periods of therapy, as was carried out in this study, did not occur.

SUMMARY

Hemolytic streptococci isolated from the nasopharynx of 40 patients, before and after sulfadiazine therapy, were tested for resistance to the action of sulfadiazine. None of the hemolytic streptococci, isolated following a course of sulfadiazine therapy, showed any evidence of the development of resistance to sulfadiazine.

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PATHOLOGIC FINDINGS IN A FATAL CASE OF DISSEMINATED GRANULOMA INGUINALE WITH MILIARY BONE AND JOINT INVOLVEMENT

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In granuloma inguinale—a disease characterized by granulomatous ulcerations of the genitalia and caused by an organism known as the "Donovan body"— the occurrence of extragenital and extrainguinal lesions has been well recognized. In previous communications (1, 2) we reported the occurrence of granuloma inguinale as a systemic disease with osteomyelitic and arthritic manifestations. The disease terminated fatally in one patient with such systemic involvement, and complete autopsy studies were made.

No complete detailed pathologic reports were found on fatal cases of disseminated granuloma inguinale, although Hoffman (3) recorded a fatal case with abscesses in bones, liver, and lungs; Kuhn (4) recorded a case with involvement of the bones, liver, and spleen; and Becker (5) referred to a case in which lesions were found in the ribs and intestinal tract at autopsy. The histology of granuloma inguinale has been ably discussed by Pund and Greenblatt (6).

Because granuloma inguinale is being seen with increasing frequency in the United States it is felt that the findings in the present case are of value in demonstrating further that granuloma inguinale is a general systemic disease which can terminate fatally; in contributing to the picture of the pathologic processes of the disease; and in reporting the occurrence of one kind of polyarticular arthritis in which a hitherto unsuspected organism was demonstrated to be the causative agent (1, 2).

CASE REPORT

The patient, a young adult colored female, died ten months after the appearance of the original genital lesion, and eight months after the onset of the systemic manifestations. In this case Donovan bodies were grown in continuous tissue cultures of material taken by biopsy

FIG. 1. BODY OF PATIENT WITH FATAL GRANULOMA INGUINALE
Note multiple granulomatous ulcerations

from affected bones and joints, as well as being demonstrated in the tissues on microscopic examination. The intimate clinical and laboratory details in this case have been reported previously (1, 2).

Autopsy Findings

Gross examination (*# 18867*). The body is that of a markedly emaciated, young adult, colored female. Weight 30 kilograms. Length 164 centimeters. Over

the forehead on the right there is a fluctuant tumor mass, and the underlying bone is eroded almost through the inner table of the skull. The cartilages of the ninth

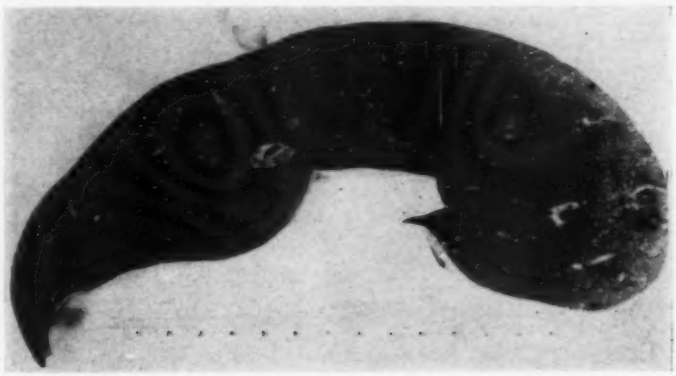

FIG. 2. GROSS SECTION OF LIVER SHOWING DISSEMINATED MILIARY ABSCESSES

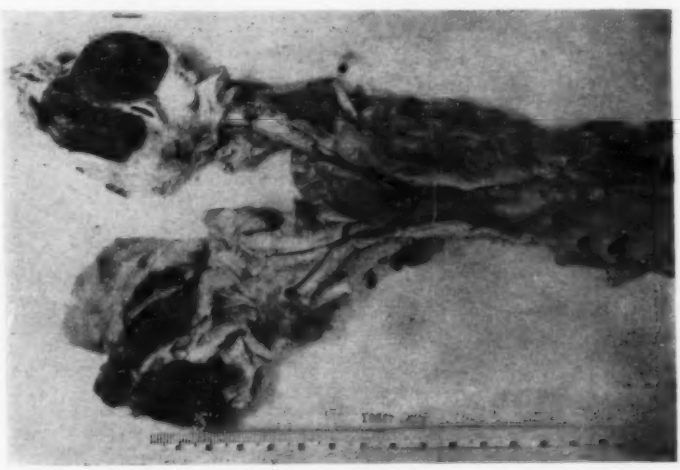

FIG. 3. AORTA AND ILIAC ARTERIES WITH INVOLVEMENT OF REGIONAL LYMPH NODES

and tenth ribs in the anterior axillary line are visible through an ulcer in the overlying soft tissues. There are large fluctuant swellings about the left shoulder joint, the right acromioclavicular joint, both elbows, both wrists, both knees, and

all the interphalangeal and metacarpophalangeal joints. There are numerous ulcerations over the body involving the back, the right olecranon, the right first

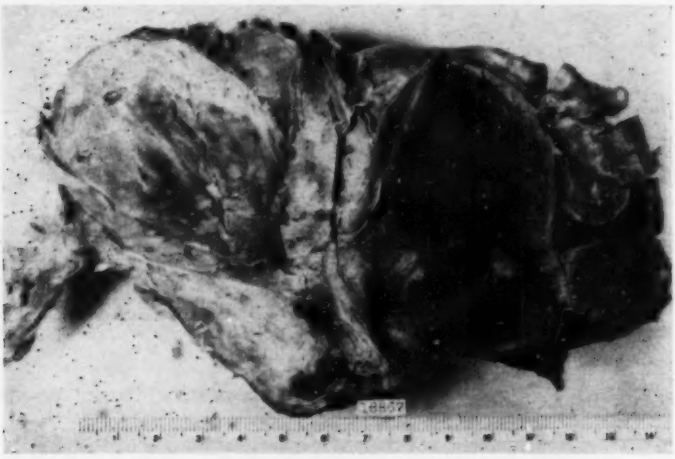

FIG. 4. UTERUS, OVARIES, AND FALLOPIAN TUBES
Note massive involvement of these tissues

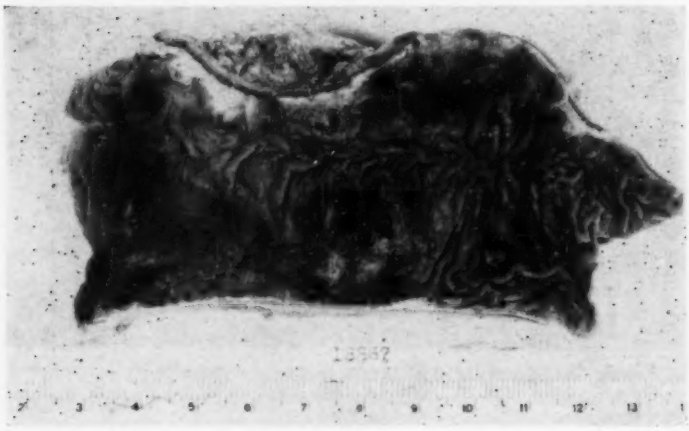

FIG. 5. LARGE BOWEL SHOWING EXTENSIVE ULCERATION OF THE MUCOSA

and second metacarpophalangeal joints, the distal interphalangeal joints of the left index and right middle fingers, the right anterior superior iliac spine, the wing

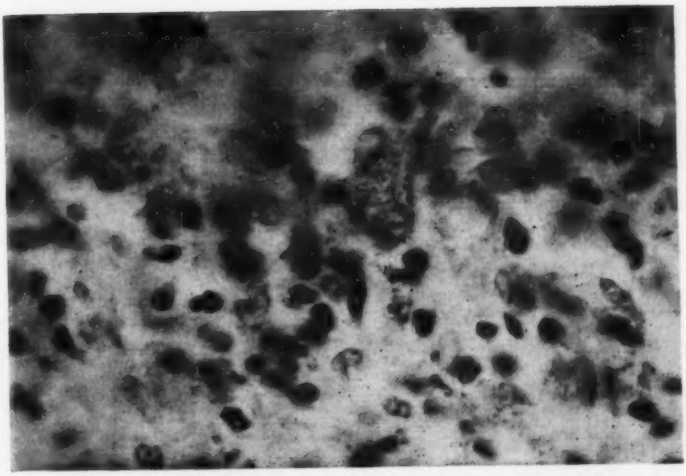

FIG. 6. (× 1400) MICROSCOPIC SECTION OF HILAR LYMPH NODE
Note numerous mononuclear cells containing Donovan bodies

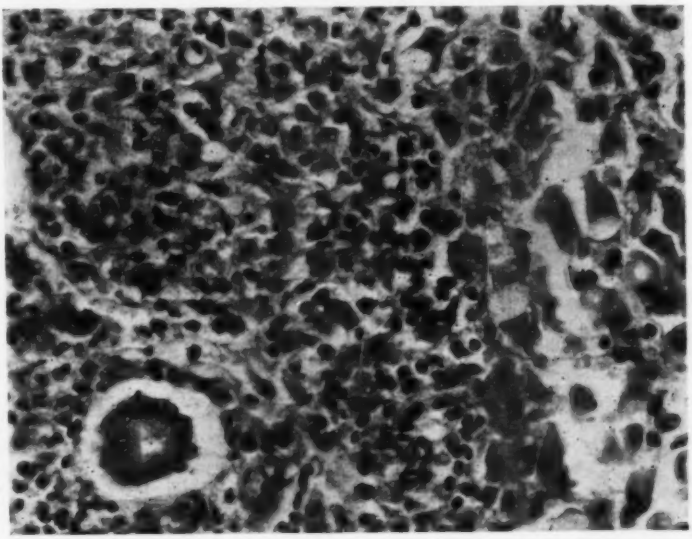

FIG. 7. (× 500) MICROSCOPIC SECTION OF LIVER THROUGH TUBERCLE-LIKE ABSCESS CONTAINING MONONUCLEAR CELLS FILLED WITH DONOVAN BODIES
Refer to Figures 6 and 11 for demonstration of the intracellular organisms under high magnification.

of the left pubic bone, the superior portion of both tibiae, the right first and fifth toes, the left first metatarsophalangeal joint, the left ankle, both heels, and the lateral side of the left foot. The left third toe has been amputated. All these ulcerated areas appear granulomatous in character.

The vagina, perineum, anus, and distal portion of the rectum are completely eroded away leaving a ragged, necrotic, foul-smelling cavity.

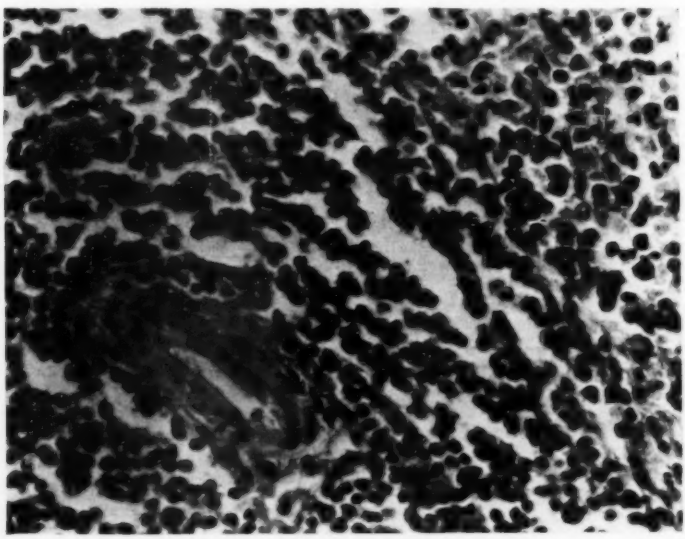

FIG. 8. (× 500) MICROSCOPIC SECTION OF SPLEEN

Note collections of mononuclear cells containing Donovan bodies. Refer to Figures 6 and 11 for demonstration of intracellular organisms under high magnification.

The lungs show a small, yellowish, rather translucent nodule 3.5 centimeters in diameter in the anterior portion of the right lower lobe near the hilum and near a good-sized bronchus.

The liver weighs 1650 grams. The capsule is thin, and scattered over it are numerous tiny gray areas about 2 millimeters in diameter. On section of the liver there appear small grayish nodules about one millimeter in diameter disseminated throughout the liver.

The spleen weighs 190 grams. Scattered over the thin, tense capsule are many tiny gray areas like those seen in the liver. On section the pulp of the spleen appears gray, and throughout are a multitude of tiny grayish-yellow nodules.

In the lower colon and the rectum the walls are thickened, and the mucosa shows extensive ulceration. The edges of the ulcer are somewhat undermined and red, and the muscularis can still be seen on the cut edges of the ulcer. No lesions are seen in the small intestine, stomach, duodenum, pancreas, or kidneys.

The left ovary and Fallopian tube are bound together to form a solid mass which on section consists of a firm yellowish material interspersed with bands of grayish scar. The right Fallopian tube is enlarged with the lumen obliterated by yellowish tissue. The right ovary is enlarged and invaded by the same yellow

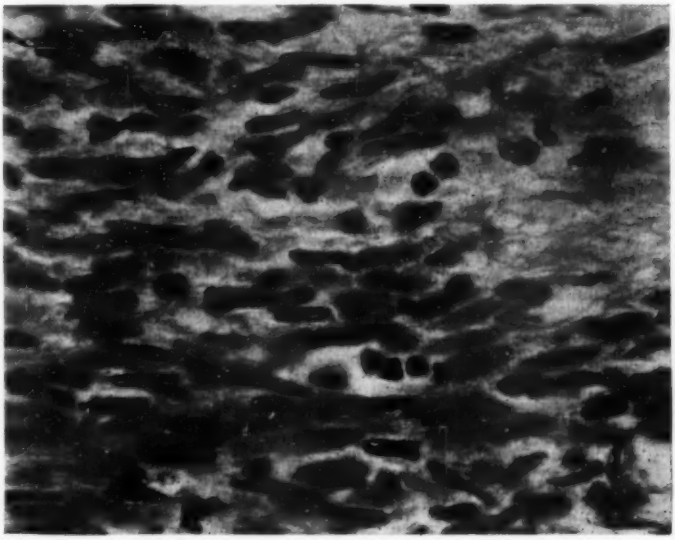

FIG. 9. (× 500) MICROSCOPIC SECTION OF PELVIC LYMPH NODE

Note masses of mononuclear cells containing Donovan bodies, and occurring in elongated forms in criss-crossing bundles. Refer to Figures 6 and 11 for demonstration of intracellular organisms under high magnification.

ish tissue. The lining of the uterus is extraordinary. It is soft, fairly smooth, and has a brilliant yellow color like fresh arteriosclerotic plaques; and this yellow coloration extends deeply into the wall of the uterus. The cervix uteri is reddened with several small granulomatous ulcers on the vaginal surface. Most of the vagina is eroded away.

At the hilum of the lungs on each side there is a single small black lymph node in which on section there are seen irregular grayish-yellow nodules. Below the level of the diaphragm all the periaortic lymph nodes are enlarged and filled with

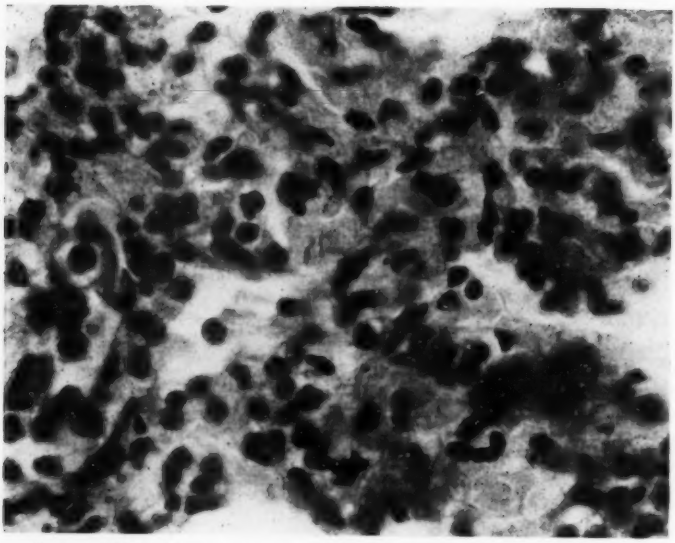

FIG. 10. (× 500) MICROSCOPIC SECTION OF LUNG THROUGH NODULE WITH MONONUCLEAR CELLS CONTAINING DONOVAN BODIES

Refer to Figures 6 and 11 for demonstration of the intracellular organisms under high magnification.

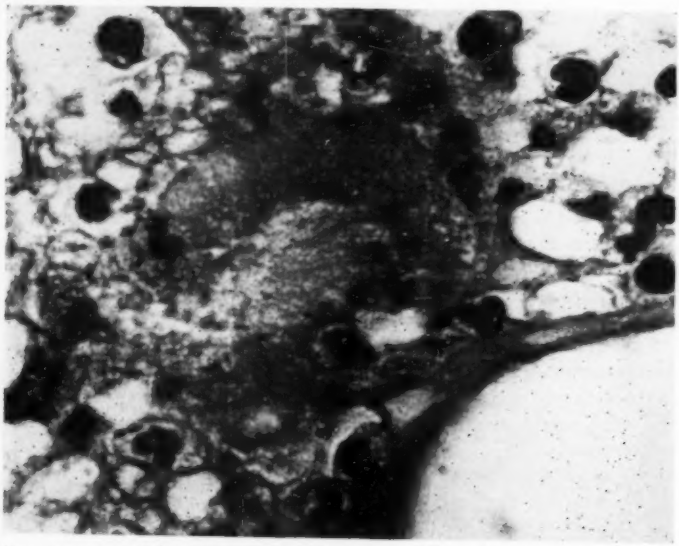

FIG. 11. (× 1400) MICROSCOPIC SECTION OF BONE SHOWING ONE LARGE MONONUCLEAR CELL CONTAINING ENCAPSULATED DONOVAN BODIES

yellowish tissue with areas of necrosis. At the distal end of the iliac and femoral specimens there is a mass on each side composed of lymph nodes surrounded by scar tissue. There are enlarged lymph nodes about the hilum of the liver, and on section these appear gray and uniform. The mesenteric lymph nodes are small with no apparent focal lesions.

The brain and meninges show no gross abnormalities.

Microscopic examination. The sections show the lesions listed in the gross examination. The foci infected by the Donovan bodies consist of great numbers of closely-packed mononuclear cells which are foamy in appearance and are evidently full of lipoid. These cells have the characteristics of the cells described by Pund and Greenblatt (6) as pathognomonic of granuloma inguinale. The lymph nodes are completely destroyed and replaced by these cells where they grow to form elongated narrow cells which form criss-crossing bundles almost like a fibrous tissue tumor. In the liver, spleen, bone marrow, and bronchial lymph nodes there are miliary abscesses which contain some of these cells and other pyknotic necrotic cells and nuclei. The endometrium, Fallopian tubes, and ovaries are extraordinarily infected and contain myriads of these foamy cells. In sections of tissues stained with Giemsa stain there appear in the cytoplasm of the foamy cells granular, bluish-stained forms corresponding to the Donovan bodies.

SUMMARY

The pathologic findings in a fatal case of granuloma inguinale are detailed. These findings are a further demonstration that granuloma inguinale is a general systemic disease which does involve bone, joints, soft tissues, internal organs; and can terminate fatally.

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PROCEEDINGS OF THE MEETINGS OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in Hurd Memorial Hall, January 14, 1946

Experimental Transmission of Japanese B. Encephalitis by Mosquitoes and Mosquito Larvae. HORACE L. HODES (*Department of Pediatrics*).

In July, 1945, an outbreak of encephalitis occurred on Okinawa. The Japanese B. encephalitis virus was shown by means of the complement-fixation test to be the cause of this outbreak. Evidence was obtained that horses as well as human beings were affected by the virus. Because mosquitoes had been suspected as the vector involved in the transmission of the disease, attempts were made in the laboratory to transmit these disease by these insects.

Mosquitoes of the species Culex *jepsoni*, Culex *quinquefasciatus* and Aedes *vexans* were employed. Adult females of these species were fed material containing the Okinawan strain of the Japanese B. virus and kept at temperature of 30 degrees centigrade for seven to thirteen days. At the end of this time the mosquitoes were afforded the opportunity of biting infant mice. After an incubation period of six to eight days, these mice developed symptoms of disease of the central nervous system and a virus which was identified as the Japanese B. encephalitis virus was recovered in each instance. Successful transmission of the disease was obtained obtained with adult females of each of the three species of mosquitoes.

Experiments were also carried out to determine whether mosquitoes, which were exposed to the Japanese B. virus in the larval stage of their life cycle could on reaching adulthood transmit the disease to mice. Second and third instar larvae of the species C. *jepsoni* were placed in water containing a 1–10,000 dilution of Japanese B. encephalitis virus for a period of eight hours. They were then washed with 5 liters of distilled water and placed in the incubator at 30 degrees centigrade where they were permitted to complete their life cycle. After they emerged as adults the females were given the opportunity of biting infant mice. A number of these latter animals developed symptoms of central nervous system disease and a virus which was identified as the Japanese B. encephalitis virus was isolated from their brains. This experiment was repeated with the same result.

Discussion

Dr. Arnold Rich: All of us are filled with admiration for the beautiful and very important studies which Dr. Hodes has presented. One point that interests me is the cross reaction between the West Nile and Japanese B. Viruses. Did you do any neutralization tests?

Dr. Hodes: Dr. Smithburn reported that the serum of a patient convalescent from St. Louis virus did neutralize West Nile virus.

Dr. A. M. Fisher: You spoke of some vaccines having been sent out there. I wonder how they were prepared, and whether they were effective in producing immunity.

Dr. Hodes: That is an Army project so I know little about it.

Dr. W. H. Barker: I was fascinated by Dr. Hodes' statement about feeding the mosquitoes without getting their feet dirty. Could you divulge how this was accomplished?

Dr. Hodes: The virus was kept away from the mosquitoes by two layers of bobinette. They stuck their noses through this and sucked up the material.

Motion Sickness. DR. PHILIP BARD (*Department of Physiology*).

Early in the War when it became apparent that the moving of large numbers of men by sea and by air to and through combat areas might be attended by high rates of motion sickness, and consequently a loss of efficiency at critical times, the problem of this common disorder began to receive, for the first time, comprehensive experimental attention.

The work on the problem done under the auspices of the Committee on Medical Research and of other agencies in this country, Canada, England and Australia was briefly outlined. The most pressing need was the development of a pharmacological preventive which, taken by mouth, would suppress the disorder for about eight hours in the majority of susceptible individuals without producing undesirable side effects. The many difficulties encountered in securing adequate field tests of a number of possible prophylactic agents were finally overcome. Chiefly as a result of tests carried out by Tyler on more than 15,000 troops undergoing amphibious training, it can be said that hyoscine alone or in combination with hyoscyamine or a barbiturate affords a 60 per cent protection when the placebo rate is as high as 50 per cent. A placebo given to large unselected groups exerts no effect. This general conclusion is in accord with results obtained by Lilienthal and others working with airsickness.

A series of experiments on dogs carried out in the Department of Physiology in collaboration with Drs. C. N. Woolsey and R. S. Snider were directed toward an analysis of the central nervous mechanisms involved in motion sickness. A basic consideration was the well-established fact that inactivation of the labyrinths renders both animals and human beings wholly immune to motion sickness. First it was found that bilateral removals of the main functional areas (motor and somatic sensory, visual, auditory) exert no influence on the susceptibility of dogs to swing sickness. The effect of complete decortication was not determined. Complete decerebellation or removal of only the nodulus and uvula rendered very susceptible dogs wholly immune to motion sickness, but did not influence the emetic response to apomorphine. It appears that the vestibular portions of the cerebellar cortex contain neural mechanisms which are prepotently involved in the

genesis of motion sickness in dogs. Ablation of certain other portions of the cerebellar cortex had no such effect.

DISCUSSION

Dr. Stacey Guild: This paper is extremely interesting, of course, to all of us. I should like to ask two questions: first, is there any evidence of the connection from the cerebellar portions of the vestibular system to the vomiting center? Second, how often can one repeat the dose of 0.6 mgm. hyoscine without trouble?

Dr. Bard: I cannot answer either question. Reports have come to the Committee of instances in which the medication was kept up for a couple of weeks without any untoward effects, provided they do not take too much. We were rather surprised that the prophylactic effect of hyoscine lasts as long as it does. In some of Tyler's experiments on landing barges, the men were delayed in getting ashore and delayed in getting off the transports for ten or twelve hours. We had assumed that four hours was the limit. I know there are a number of people in the Army who have either themselves taken the capsules over long periods of time or have administered them to others. Maybe some are present. I think Dr. Hellman did an experiment on this.

Dr. Otenasek: In view of the results obtained in dogs, I wonder what Dr. Bard would say to an experiment in which this operation is carried out following section of the vestibular nerve. Does this area of the cerebellum have anything to do with the possible treatment of Meniere's disease?

Dr. Bard: I would like to know and I think it would be worth finding out. In Meniere's disease the symptoms are so tremendous that if anything could be done to ameliorate them, it would be important. I would not make a prediction, however. I think it would be rather interesting and also important—even justifiable—to try the removal of these vestibular cerebellar structures in humans with Meniere's disease for this reason—the general disturbances (I have not mentioned them at all in connection with the experiments on dogs and in monkeys) which result from their removal are minimal and I would judge very much less than those produced in patients by section of one or both vestibular nerves. That is one thing I hope one of you finds out soon.

PROCEEDINGS OF THE MEETINGS OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in Hurd Memorial Hall, February 11, 1946

Chemotherapy of Malaria, 1941–1945. DR. E. K. MARSHALL, JR. (*Department of Pharmacology*).

Malaria Experiences in the Southwest Pacific. COLONEL BENJAMIN M. BAKER, M.C. (*Department of Medicine*).

DISCUSSION

Dr. Gilbert F. Otto: I would like to ask Colonel Baker, in the group in the last chart, is three months after therapy an adequate period in which to determine occurrence?

Colonel Parker: I can answer that by saying that in thousands of cases infected by the Guadalcanal strain of vivax, the intervals separating relapses average 35 days. This is entirely different in the Southeastern United States vivax where the intervals may be eight or nine months. You are perfectly correct; it is unfortunate that we could not follow our patients any longer. Every man was given a card upon which to report malaria attacks in the next two years. So far, out of 800 men, I have received only three letters. The peak of the relapses comes in the sixth week with the Guadalcanal strain. For that reason I think that a three months' period of observation, while not perfect, is certainly significant.

Dr. Warfield T. Longcope: I would like to ask Dr. Marshall or Colonel Baker whether atabrine has the same effect in vivax malaria as in falciparum malaria when given in suppressive doses?

Colonel Benjamin M. Baker: Let me answer first because I think this last chart demonstrates that atabrine has approximately the same effect in vivax malaria in suppressive doses as in falciparum with few exceptions, provided you give it long enough; but we know that six months is not long enough. It happens that this was for eighteen months because we could not stop the drug sooner. What would have happened if it had been for six, nine or twelve months, I do not know; but I think it has the same effect in most cases of vivax when given for a long time as it has in falciparum when given for a short time.

Dr. E. K. Marshall: The troops were not given adequate suppressive treatment on Guadalcanal, were they?

Colonel Benjamin M. Baker: They were given suppressive treatment. On Guadalcanal they had common diarrhea, outbreaks of dysentery, got yellow and

had infectious hepatitis at the same time. The soldiers wonder what atabrine had to do with conditions. They would say: "The officers take quinine; why do we take atabrine? There must be something wrong." This brought about complete deterioration in atabrine discipline. It was two years before we thought we had facts enough to show that the reason it did not work was because the men were not taking it. However, that is not invariably so, as we have brought out.

Dr. Marshall: I would like to emphasize that again. I think you can not be sure the men are getting atabrine unless you see them taking it, and even then they will hide it in their mouths and spit it out an hour later.

Brigadier Fairlee told me that, in the Australian Army, if the malaria rate went above a certain figure in a certain area, the general was relieved.

Colonel Baker: I would like to emphasize that fact also. I should have discussed it but had to hurry. Some or our results are not in agreement with those of Brigadier Fairlee: that is, about suppression of falciparum malaria. As I tried to point out, with one strain it worked 100% with volunteers; but he was not working with the Bougainville strain; and although he was making the men hike, taking them up in planes and so on, they were not subjected to conditions precisely the same as conditions of combat. When I got back to this country, I was told about plasmoquin. Men were given 30 mgm. of plasmoquin a day for two weeks and no one objected, but you can not do that in overseas forces. They get pain, nausea and vomiting not in an occasional man but hundreds. Just what the difference is in giving it in this country and an overseas hospital, I do not know; but it has been observed too widely not to be a fact. Most of our men had had diarrhea, had lost weight, were under high nervous tension and wanted to go home.

Dr. Alexander J. Schaffer: I don't think I have anything to add to this excellent discussion by Dr. Marshall and Colonel Baker. I would like to say in respect to plasmoquin that I brought that question up with General Biggam in India. He was aware that certain troops in certain parts of the world had more toxic reactions to plasmoquin than others and had only one explanation to offer. Some of the pills had been taken back to the laboratory and were found to contain from 15 to 17 mgm. rather than 10 mgm. of the drug so that some men were getting as much as 51 mgm. a day. That may be the whole answer and may not be. Certainly we have had whole wards full of boys with "plasmoquin bellies" in troops presumably taking 30 mgm. per day.

I do disagree to a minor extent on the matter of percentage protection. Brigadier Fairley claimed that 100% would be taken care of with one tablet of atabrine a day. We feel sure, on theoretical grounds and also from observation, that men will break through with malaria occsionally, even though they take 1 tablet daily. The theoretical basis seemed to us completely understood. Almost all of the men who break through suppression and develop relapses break through with very low levels. However, very occasionally men relapse with 20–30 mic./L. Since a small number of men cannot achieve levels of even 10 mic./L., and since break-

through can, rarely, occur at levels of 20 and above it is obvious that 100% will not be protected. For all practical purposes, however, one can assume that 1 tablet a day will protect.

Dr. Marshall: I know of no evidence that will show that on a given daily dose—where you are absolutely sure everyone is taking it—the break-through will have a low level. I don't think anyone has that evidence.

Dr. Schaffer: Even though they have very low levels, they will not develop malaria.

Dr. Marshall: There is no real evidence that the plasma level has anything to do with it. Most people in this country say, of course, that the plasma level is important.

Dr. Schaffer: I guess I can say that if it is not important, it looks very much as if it is.